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In Dubio Pro Therapia: Unexpected Recovery after Palliative Endoscopic Third Ventriculostomy and Temozolomide Chemotherapy in a Patient with Progressive Glioblastoma multiforme

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Abstract

A 38-year-old female with a 7-year history of recurrent high-grade astrocytoma was admitted to our institution presenting with progressive signs of increased intracranial pressure. MRI showed widespread tumor recurrence with diffuse infiltration of the ventricular walls, basal cisterns and concomitant hydrocephalus. After careful consideration a palliative endoscopic third ventriculostomy was performed. After surgery the patient's condition improved significantly. Thus far she had only undergone radiation, therefore now chemotherapy was initiated. After 4 courses of Temozolomide a follow-up MRI showed no pathologic contrast enhancement. Six months later the patient is still alive in good clinical condition (KPS 90%).

Keywords

Secondary Glioblastoma, Endoscopic ventriculostomy, Long-term survivor, Palliative

Introduction

Despite all therapies, the prognosis of high-grade astrocytomas is poor. Adjuvant therapies are known to prolong life, but so far no cure is available [1]. Occasionally the clinical course is less aggressive than expected and tumors respond surprisingly well to adjuvant treatment, which might be due to their histopathologic heterogeneity and their specific genetic profile [2].

The median age at diagnosis is 64 for glioblastomas and 45 years for anaplastic astrocytomas [1]. Especially the younger patients are often in the middle of their lives.

Just like our patient: the 32-year-old woman was 14 weeks pregnant when diagnosed with a malignant brain tumor, which greatly influences her approach towards treatment. Here we report her extraordinary clinical course.

Case Presentation

Due to intermittent dyslexia with dysphasia and progressive headache, an MRI was performed showing an inhomogeneous, partially cystic lesion in the left parieto-occipital lobe with surrounding edema and space occupying effect. No contrast agent was applied due to the patient's pregnancy (Figure 1). The first surgery for reduction of intracranial pressure and histopathological evaluation was performed in August 2009 while preserving the pregnancy. Histopathological evaluation showed a high-grade astrocytoma without clear-cut necrosis and with a Mib-1 proliferation rate of 15%. However glioblastoma multiforme was diagnosed, since definite vascular proliferations were seen (Figure 2(a, b & d) [3,4]. The standard combined radio-chemotherapy [5] was primarily postponed due to the patient's pregnancy, but later declined by the patient herself.

In 2011, growth of the residual tumor was noticed with inhomogeneous contrast-enhancement and re-operation was performed with complete resection (Figure 3). Histopathological evaluation showed recurrence of the high-grade astrocytic tumor. Standard radio-chemotherapy was recommended again. However, based on the patient's requests only radiation (RT) was performed. The former tumor bed region including a peripheral safety margin was defined as planning target volume. The patient was treated with conformal RT using three non-coplanar wedged 6 MV photon fields. The total dose was 60 Gy with 2Gy per fraction. Planar sections of the isodose plan are shown in figure 4(a-d).

Follow-up MRI in 2014 showed stable conditions at the primary tumor site without signs of recurrence, but a new intraventricular manifestation. Complete resection was achieved using an endoscopic technique (Figure 5). Histopathological evaluation confirmed secondary glioblastoma WHO IV (IDH-1 positivity, retained nuclear ATRX, no loss of 1p19q, MGMT methylated, MIB-1 70%; Figure 2(c,

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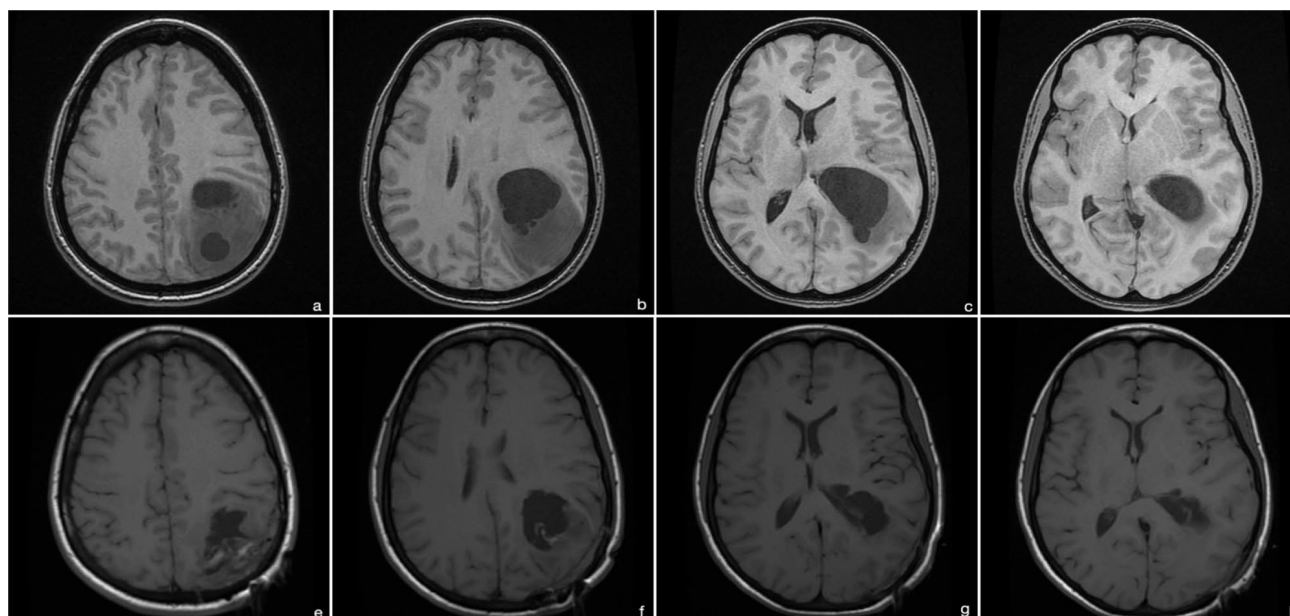


Figure 1: MRI 2009 (t1 without contrast due to pregnancy). (a-d) preoperative images: cystic, intraaxial lesion in the left parieto-occipital lobe; postoperative images: partial tumor resection; (e-h) postoperative images showing partial tumor resection.

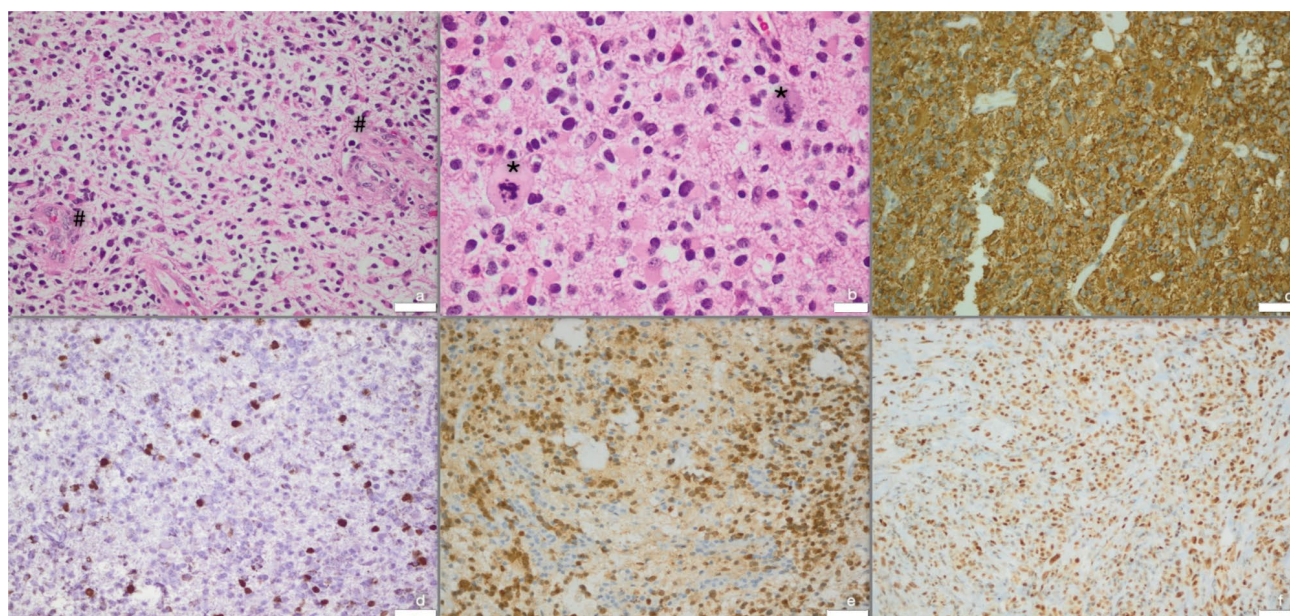


Figure 2: Histology of surgical specimen from respective years. (a) 2009: HE-stain - vascular proliferation (#); (b) 2009: HE-stain - atypical mitoses (*); (c) 2014: GFAP; (d) 2009: MIB 15%; (e) 2014: IDH1; (f) 2014: ATRX; Scale bars for a, c, d, e, f 50 µm, for b 20 µm.

e & f)). Adjuvant radio-chemotherapy with adapted radiation-volume was planned. The treatment planning volume including isodose distribution is displayed in figure 4(e-h). A volumetric modulated arc therapy (VMAT) with 6 MV photons for dose minimalization in the pre-irradiated brain region was applied. Due to side effects, the patient refused further treatment after only 3 radiation-sessions (6 Gy). Concomitant chemotherapy was rejected again.

In May 2015, she was admitted with progressive headache and rapid deterioration of her vigilance. MRI revealed severe tumorprogression with diffuse infiltration of the ventricular walls and the basal cisterns (Figure 6(a-d)) with secondary, occlusive hydrocephalus. After thoroughly discussing treatment options and the patient's wishes with the family a palliative endoscopic third ventriculostomy (ETV) was performed (Figure 7, Video 1 - supplement). Pathological evaluation of the cerebrospinal fluid (CSF), collected during surgery, revealed multiple cells of the previously diagnosed glioblastoma, confirming diffuse tumor progression. Yet, the patient's clinical condition improved rapidly after surgery, leading to the assumption that her preoperative condition was

mainly due to hydrocephalus and not tumor progression. Thus, despite the highly unfavorable prognosis chemotherapy with temozolomide was initiated (160 - 200 mg/m² BSA, 6 cycles, 5/28). While undergoing therapy the patient's condition further improved. A follow-up MRI in September 2015, after 4 cycles of chemotherapy, showed marked regression of the tumor without any contrast enhancing tumor remnants (Figure 4 (e-h)). Six months after surgery the patient is still alive in good clinical condition (KPS 90%).

Discussion

With increasing knowledge about genetic variations within astrocytomas, diverging clinical courses despite similar microscopic appearance can be explained [1,2,6-8]. This case, despite showing histopathological features of a glioblastoma °IV as defined by "The 2007 WHO Classification of tumors of the central nervous system" [3,4] diagnosed at two different pathological institutes, illustrates the difficulty with the existing classification. It has become known over the past years that molecular profiles might be more relevant

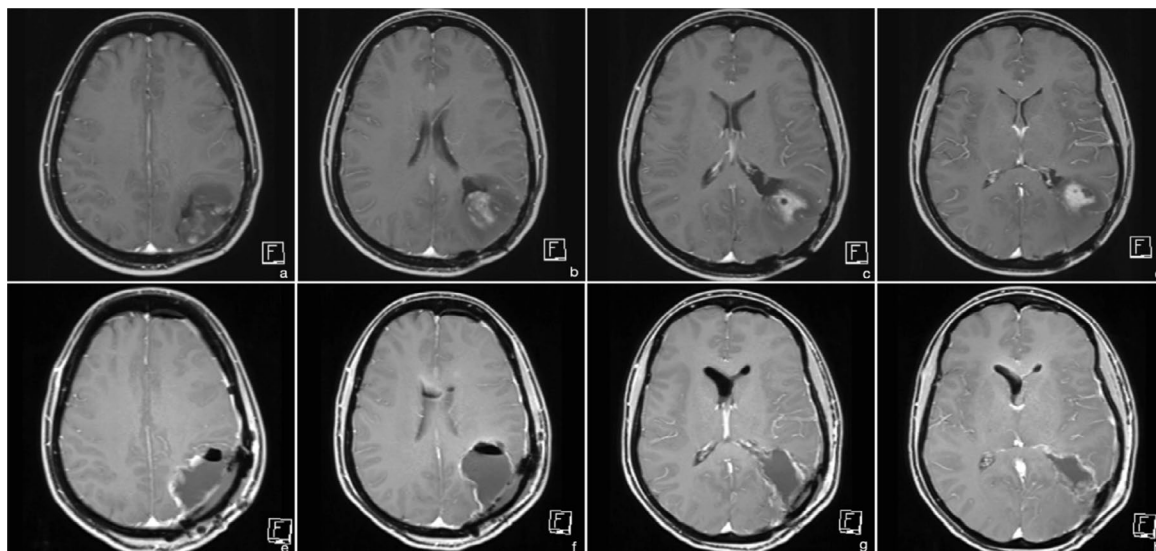


Figure 3: MRI 2011 (t1 with contrast). (a-d) preoperative images - partially contrast enhancing lesion; (e-h) postoperative images - complete resection.

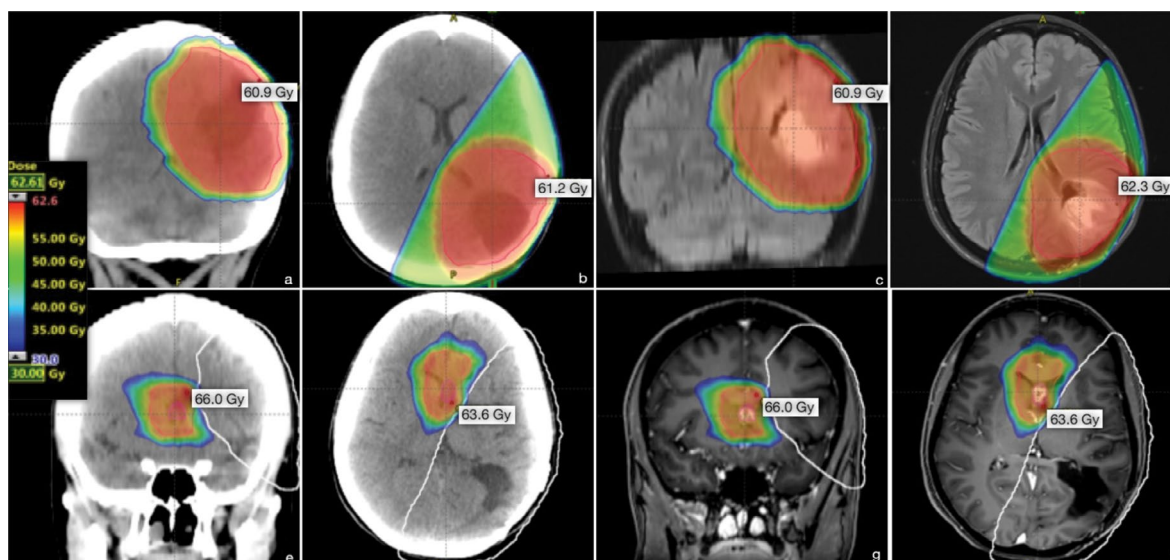


Figure 4: Radiation Target Volume and isodose distribution (axial, coronal). (a, b) post-surgery CT projections (2011); (c, d) corresponding projections in the coregistered (fused) preoperative MRI (2011); (e, f) post-surgery CT projections (2015); (g, h) corresponding projections in the coregistered (fused) preoperative MRI (2015); (e-f) The bright white line marks the region which has received ≥ 20 Gy in the first course.

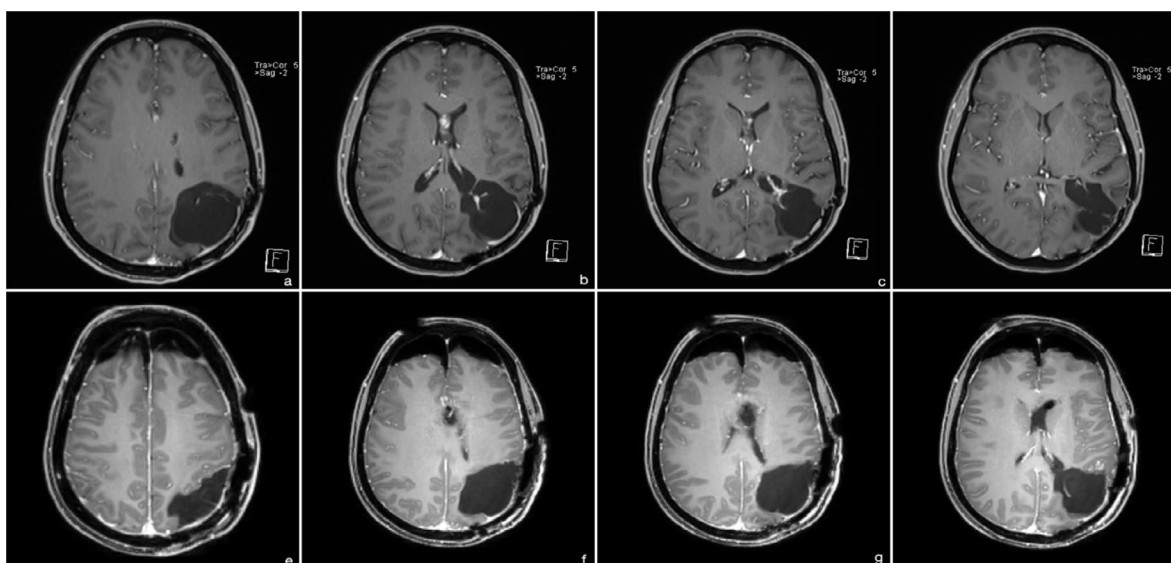


Figure 5: MRI 2014 (t1 with contrast). (a-d) preoperative images - secondary intraventricular manifestation without signs of recurrence at the primary site; (e-h) postoperative images - complete resection.

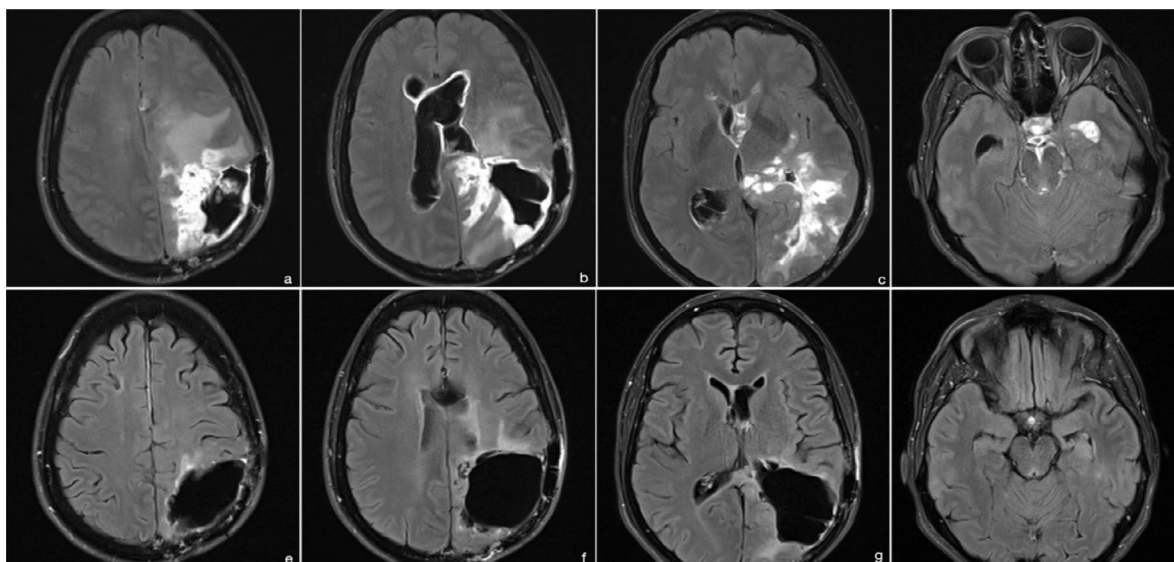


Figure 6: MRI 2015 (t2 flair with contrast). (a-d) preoperative images - diffuse infiltrative tumor growth with enlarged ventricles; (e-h) images after ETV and 4 cycles of temozolomide-treatment - tumor regression without pathologic contrast enhancement, normalized ventricular walls.

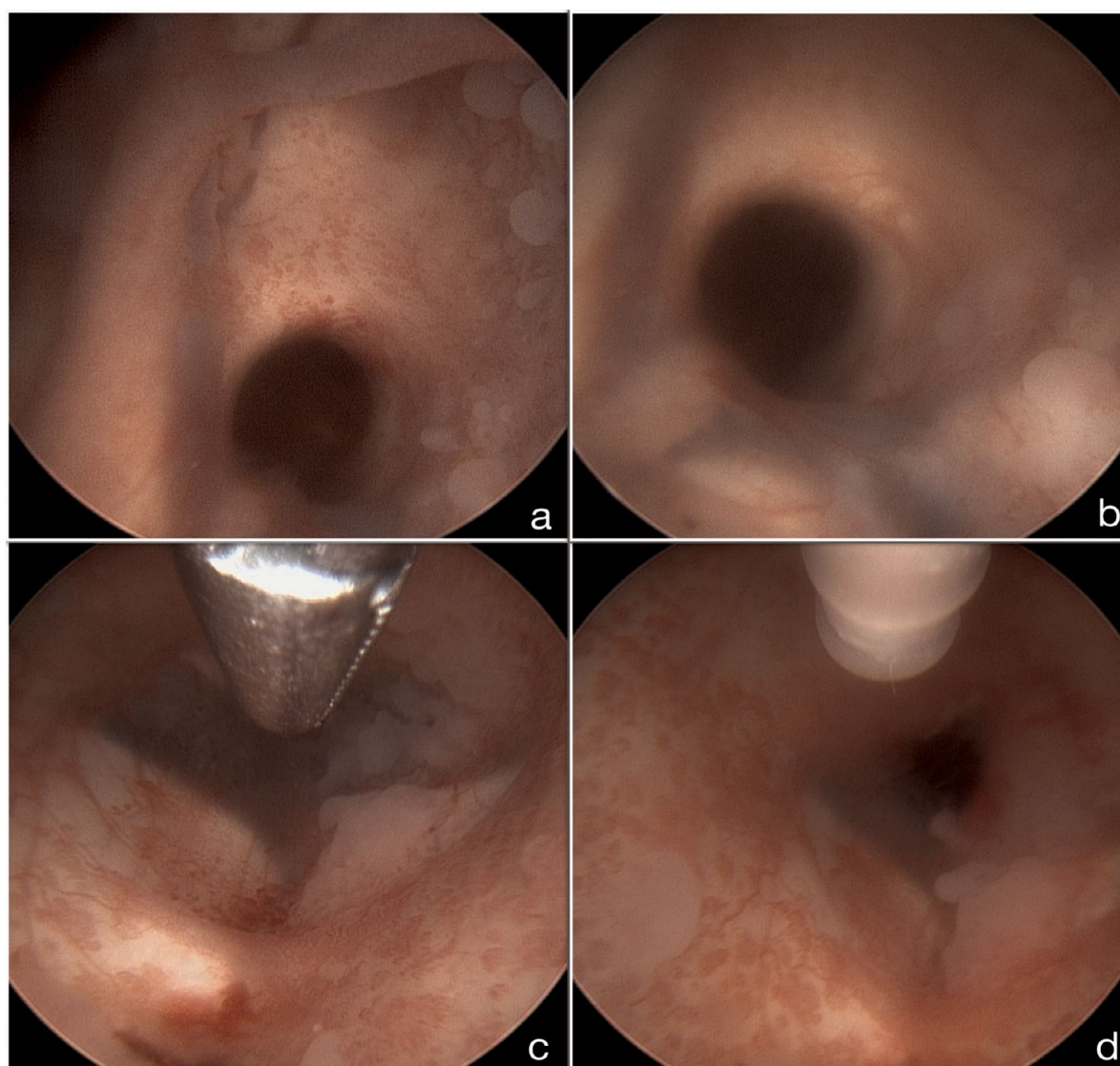


Figure 7: Intraoperative Endoscopic Images. (a, b) Ventricular wall infiltration around Foramen of Monroi; (c) Floor of the 3rd ventricle before perforation; (d) Floor of the 3rd ventricle after perforation.

towards prognosis than microscopic patterns [2,7] calling for a new classification.

Even though the tumor did presents with a favorable molecular profile (secondary malignisation (IDH1 pos), MGMT methylation, ATRX retained) [1,8] the effect of chemotherapy was not expected

in this case. Yet, it shows that patients presenting with occlusive hydrocephalus and signs of raised intracranial pressure should be considered for treatment of the hydrocephalus according to the clinic's standard to allow for a differentiation of symptoms caused by hydrocephalus and those caused by tumor progression itself, especially if further adjuvant treatment is still available. In cases of occlusive hydrocephalus, ETV poses an elegant option for treatment. The patient does not need prolonged external drainage with its associated risk of dislocation and infection and no foreign material needs to be placed as with a shunt. Furthermore, in cases of shunt placement, a high failure rate could be expected due to increased protein and cell count in the CSF.

One could argue that extensive therapy in a patient, who refused several treatments along the way, is not warranted. But due to the disease, her judgment may have been impaired as intracerebral tumors are known to cause cognitive deficits, which in turn influences treatment decisions [9,10], but may improve over time [11]. When being confronted with a life-threatening disease, maintaining quality of life is important and thus, some patients may refuse adjuvant treatment due to its side effects.

The response witnessed after chemotherapy might partially be due to the tumors favorable molecular profile (MGMT methylated, IDH 1 positive) [1,2,8,12], but also due to its temozolomide naivety. Furthermore, the widespread infiltration may have lead to a vast breakdown of the blood-brain barrier, allowing for better penetration of the chemotherapeutic agent. This further underlines, if patients change their opinion towards treatment during the course of the disease and treatment options are still available, even controversial measures should be considered.

Conclusion

Patients with malignant brain tumors who present with tumor progression and coinciding hydrocephalus should be considered for treatment of the hydrocephalus in order to distinguish the causes of their deterioration, especially if standard treatment options are still available. Furthermore, ETV poses a smart technique for the

treatment of occlusive hydrocephalus without the need for insertion of external drainage or a VP-shunt.

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